

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 November 1997 (06.11.97)	
International application No. PCT/GB97/01007	Applicant's or agent's file reference RFB/P98565WO
International filing date (day/month/year) 11 April 1997 (11.04.97)	Priority date (day/month/year) 12 April 1996 (12.04.96)
Applicant KRANJC, Sasa et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
20 October 1997 (20.10.97)

☐ in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  A. Addae-Ruesch  Telephone No.: (41-22) 338.83.38
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09/171/081

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BROWNE, Robin, Forsythe  
Urquhart-Dykes & Lord  
Tower House  
Merrion Way  
Leeds LS2 8PA  
ROYAUME-UNI

Date of mailing (day/month/year) 22 October 1998 (22.10.98)	<b>IMPORTANT NOTIFICATION</b>
Applicant's or agent's file reference RFB/P98565WO	
International application No. PCT/GB97/01007	International filing date (day/month/year) 11 April 1997 (11.04.97)

1. The following indications appeared on record concerning:

☒ the applicant
     
 ☐ the inventor
     
 ☐ the agent
     
 ☐ the common representative

Name and Address BROWNE, Robin, Forsythe Urquhart-Dykes & Lord Tower house Merrion Way Leeds LS2 8PA United Kingdom	State of Nationality GB	State of Residence GB
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person
     
 ☐ the name
     
 ☐ the address
     
 ☐ the nationality
     
 ☐ the residence

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

**The applicant indicated in Box 1 has been deleted from the record.**

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Kari Huynh-Khuong Telephone No.: (41-22) 338.83.38
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# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>RFB/P98565W0</b>	<b>FOR FURTHER ACTION</b> <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. <b>PCT/GB 97/ 01007</b>	International filing date (day/month/year) <b>11/04/1997</b>	(Earliest) Priority Date (day/month/year) <b>12/04/1996</b>
Applicant <b>LEK PHARMACEUTICAL &amp; CHEMICAL CO DD et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).

2. ☐ Unity of invention is lacking (see Box II).

3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☐ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☒ the text is approved as submitted by the applicant.  
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. \_\_\_\_\_ ☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

# INTERNATIONAL SEARCH REPORT

International Application No

CT/GB 97/01007

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C12P17/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 571 888 A (GLAXO LAB LTD) 23 July 1980 see example 1	1,2
X	EP 0 182 522 A (ANTIBIOTICOS SA) 28 May 1986 see example 1	1
X	DATABASE BIOSIS BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US DEMAIN A L: "PRODUCTION OF BETA LACTAM ANTIBIOTICS AND ITS REGULATION." XP002035710 see abstract & PROC NATL SCI COUNC REPUB CHINA PART B LIFE SCI 15 (4). 1991. 251-265. CODEN: PNBSEF ISSN: 0255-6596,	1
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\* & \* document member of the same patent family

Date of the actual completion of the international search

22 July 1997

Date of mailing of the international search report

08.08.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Delanghe, L

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/01007

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	✓ US 4 110 165 A (COLE MARTIN ET AL) 29 August 1978 see examples 5,9,12,13 ---	1
Y	✓ FR 2 328 045 A (BEECHAM GROUP LTD) 13 May 1977 see example 1 ---	1
Y	✓ US 4 144 242 A (FLEMING IAN D ET AL) 13 March 1979 see column 11 ---	1
Y	✓ CHEMICAL ABSTRACTS, vol. 95, no. 3, 20 July 1981 Columbus, Ohio, US; abstract no. 22886g, LILLEY, G ET AL.: "Control of the production of cephamycin C and thienamycin by Streptomyces cattleya NRRL 8057" page 516; XP002035709 see abstract & J.CHEM. TECHNOLOG. BIOTECHNOL., vol. 31, no. 2, 1981, pages 127-134, cited in the application -----	1

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 97/01007

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1571888 A	23-07-80	JP 52120193 A	08-10-77
		JP 60004720 B	06-02-85
		US 4155082 A	15-05-79
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EP 0182522 A	28-05-86	AU 600655 B	23-08-90
		AU 4909085 A	01-05-86
		CA 1307223 A	08-09-92
		CN 1010415 B	14-11-90
		EG 17153 A	30-06-90
		EP 0312813 A	26-04-89
		HK 26696 A	16-02-96
		IE 58365 B	08-09-93
		IN 162768 A	09-07-88
		IN 166818 A	21-07-90
		JP 6046949 B	22-06-94
		JP 61119195 A	06-06-86
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US 4110165 A	29-08-78	GB 1508977 A	26-04-78
		AR 206627 A	06-08-76
		AR 216430 A	28-12-79
		AR 219050 A	31-07-80
		AT 350718 B	11-06-79
		AT 353407 B	12-11-79
		AT 350719 B	11-06-79
		AT 348124 B	25-01-79
		AT 352270 B	10-09-79
		AU 499171 B	05-04-79
		AU 8017775 A	21-10-76
		BE 827926 A	14-10-75
		CA 1059050 A	24-07-79
		CA 1055395 A	15-05-79
		CA 1074325 A	25-03-80
		CA 1076120 A	22-04-80
		CH 629252 A	15-04-82
		CH 630631 A	30-06-82
		CS 7502721 A	13-02-84
		CY 1078 A	27-12-80
		DE 2517316 A	23-10-75
		DE 2559410 A	23-09-76
		DE 2559411 A	21-10-76

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 97/01007

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4110165 A		DE 2560074 C	28-03-85
		EG 12445 A	31-12-78
		FR 2267778 A	14-11-75
		HK 54780 A	03-10-80
		IN 140042 A	04-09-76
		JP 1054511 C	23-07-81
		JP 53002494 A	11-01-78
		JP 55049830 B	15-12-80
		JP 1054512 C	23-07-81
		JP 53002495 A	11-01-78
		JP 55049831 B	15-12-80
		JP 1054513 C	23-07-81
		JP 53003588 A	13-01-78
		JP 55049832 B	15-12-80
		JP 1054514 C	23-07-81
		JP 53003589 A	13-01-78
		JP 55049833 B	15-12-80
		JP 53003590 A	13-01-78
		JP 872874 C	29-07-77
		JP 50142789 A	17-11-75
		JP 52001996 B	19-01-77
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		JP 50142591 A	17-11-75
		JP 52046957 B	29-11-77
		JP 1008055 C	31-07-80
		JP 52085189 A	15-07-77
		JP 54043520 B	20-12-79
FR 2328045 A	13-05-77	GB 1563103 A	19-03-80
		AR 211031 A	14-10-77
		AT 354624 B	25-01-79
		AU 503529 B	06-09-79
		AU 1855576 A	20-04-78
		BE 846933 A	04-04-77
		CA 1072471 A	26-02-80
		CH 629532 A	30-04-82
		DE 2646001 A	21-04-77
		JP 1338758 C	29-09-86
		JP 52047991 A	16-04-77
		JP 60057834 B	17-12-85

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 97/01007

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2328045 A		NL 7611204 A	15-04-77
		SE 434065 B	02-07-84
		SE 7611046 A	14-04-77
		US 4072569 A	07-02-78
		ZA 7605702 A	28-09-77
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US 4144242 A	13-03-79	GB 1543563 A	04-04-79
		AT 353409 B	12-11-79
		AU 509313 B	08-05-80
		AU 1089176 A	11-08-77
		BE 838330 A	06-08-76
		CH 624956 A	31-08-81
		DE 2604697 A	19-08-76
		FR 2368276 A	19-05-78
		JP 51101994 A	08-09-76
		JP 2022281 A	25-01-90
		NL 7601227 A	10-08-76
		SE 421796 B	01-02-82
		SE 7601337 A	03-11-76
		US 4490295 A	25-12-84
		US 4367175 A	04-01-83
		US 4490294 A	25-12-84
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# PATENT COOPERATION TREATY

REC'D 21 JUL 1998

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## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RFB/P98565WO	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)	
International application No. PCT/GB97/01007	International filing date (day/month/year) 11/04/1997	Priority date (day/month/year) 12/04/1996
International Patent Classification (IPC) or national classification and IPC C12P17/18		
Applicant LEK PHARMACEUTICAL & CHEMICAL CO DD et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 20/10/1997	Date of completion of this report 17. 07. 98
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Luzzatto, E Telephone No. (+49-89) 2399-8169 

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB97/01007

## I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

### Description, pages:

1-12 as originally filed

### Claims, No.:

1-15 as received on 05/05/1998 with letter of 29/04/1998

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☒ the claims, Nos.: 16-18  
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Yes:	Claims 1-15
	No:	Claims
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-15
Industrial applicability (IA)	Yes:	Claims 1-15
	No:	Claims

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB97/01007

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2. Citations and explanations

**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/GB97/01007

**PART V**

- 1) The amendments meet the requirements of Art. 34(2)(b) PCT.
- 2) The present application would appear not to meet the requirements of Art. 33 PCT.
  - 2.1) EP-A-182522 (D1), GB-A-1571888 (D2) and US-A- 4110165 (D3) disclose a method for the production of clavulanic acid which comprises the use of suitable Streptomyces strains in the presence of a phosphorus concentration below the limit to which the present claim 1 relates (see the passages of D1 and D2 quoted in the Search Report, ex. 5 of D3); however, none of these documents teaches the use of an initial concentration of assimilable nitrogen higher than 5%. The subject-matter of claim 1 is thus novel (Art. 33(2) PCT).
  - 2.2) As to inventive step, none of the said documents, either alone or in combination with any other available document, suggest that such an initial concentration of nitrogen could be of any advantage. However, it appears that the description of the present application does not disclose any such advantage either; it merely states that it is advantageous (p. 4, l. 5-6) without providing any supporting evidence. Nowhere in the description is it indicated that the titre of clavulanic acid is optimised by using any specific concentration of nitrogen source (see p. 2, first full paragraph and p. 3, l. 2-p. 4, l. 6). Moreover, not a single example of an initial concentration of the nitrogen source higher than 5% is given.  
For inventive step of the subject-matter to be acknowledged, the applicant should have provided experimental data supporting the alleged advantages.
  - 2.3) Claims 2-15 relate to conventional features which, thus, cannot impart inventive step to the subject-matter of claim 1 on which they depend.

**PART VII**

To comply with Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/GB97/01007

documents cited in part V should have been mentioned in the description and these documents should have been identified therein.

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## CLAIMS

1. A process for production of clavulanic acid comprising fermentation of a clavulanic acid producing species of *Streptomyces* in a fermentation broth containing assimilable sources of carbon and nitrogen, wherein the concentration of assimilable phosphorus in the fermentation broth is less than 0.15% w/v.
2. A process as claimed in claim 1, wherein the phosphorus concentration is maintained below a limit of 0.15% w/v during the growth phase.
3. A process as claimed in claim 2 wherein the phosphorus concentration is allowed to decrease after cessation of the growth phase.
4. A process as claimed in any preceding claim, wherein the phosphorus concentration is allowed to decrease after a fermentation time of 40 hours.
5. A process as claimed in any preceding claim, wherein the phosphorus concentration up to a fermentation time of 40 hours is 0.0015 to 0.15% w/v.
6. A process as claimed in claim 5, wherein the phosphorus concentration is 0.002 to 0.05% w/v.
7. A process as claimed in any preceding claim, wherein no assimilable phosphorus is added after a fermentation time of 40 hours.
8. A process as claimed in any preceding claim, wherein the source of assimilable nitrogen does not include ammonia.
9. A process as claimed in claim 8, wherein the sole source of assimilable nitrogen is not ammonia.

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10. A process as claimed in any preceding claim, wherein the source of assimilable nitrogen is flour.

11. A process as claimed in any preceding claim, wherein the assimilable nitrogen source is ammonium sulphate.

12. A process as claimed in any preceding claim, wherein the concentration of the assimilable nitrogen source is 0.5 to 15% w/v.

13. A process as claimed in any preceding claim, wherein the starting concentration of the assimilable nitrogen source is greater than 5% w/v.

14. A process as claimed in any preceding claim, wherein the source of assimilable phosphorus is sodium or potassium phosphate, sodium or potassium dihydrogen phosphate or disodium or dipotassium hydrogen phosphate or a mixture thereof.

15. A process as claimed in any preceding claim, wherein the microorganism is *Streptomyces clavuligerus*, *Streptomyces jumonjinensis*, *Streptomyces katsurahamanus* or *Streptomyces* sp. P6621.

16. A process as claimed in any preceding claim, wherein the process is fed batch or continuous with intermittent or continuous addition of an assimilable source of phosphorus.

17. A process as claimed in any preceding claim, wherein the volume of the fermentation broth is greater than  $10^4$  l.

18. A process as claimed in claim 17, wherein the volume is  $5 \times 10^4$  l.